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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,855	11/02/2005	Patrick Van Berkel	089995-000000US	4048

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HIRIYANNA, KELAGINAMANE T	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
08/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,855	BERKEL ET AL.	
	Examiner	Art Unit	
	KELAGINAMANE HIRIYANNA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-9,13,16,19,20,22-26 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7-9,13,16,19,20,22-26 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 05/19/2010 in response to office action mailed on 12/24/2009 has been acknowledged.

Claims 1, 16, 17, and 25 are amended.

Claims 2-3, 5-6, 10-12, 14-15, 17-18, 21 and 27 are canceled.

Claims 2, 3, 5 10-12, 14-15, 18, and 21 were previously cancelled.

Claims 28-31 are new.

Claims 1, 4, 7-9, 13, 16, 19-20, 22-26, and 28-31*are pending and are examined in this office action.*

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Withdrawn: Claims 1, 4, 6-9, 13, 16-17, 19-20, and 22-27 rejection under 35 USC 103 (a) as being unpatentable over Wolf et al., (2001, protein expression and purification 22:414-421) and Paulson et al (1998, WO 98/31826) for the reasons of record as set forth in the office action mailed on 12/24/2009 is withdrawn in view of Applicants amendments to claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 1, 4, 7-9, 13, 16, 19-20, 22-26, and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of extending blood circulatory half-life of a recombinant human C1 inhibitor by removing or modifying O-linked carbohydrate modification in vitro of a Gal (β1-3)Gal(NAC) or Gal (β1-4)Gal(NAC) moiety is not enabled for changing the circulatory half life of any

glycoprotein using said method in vitro or in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At issue, under the enablement requirement of 35 U.S.C. 112, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based of the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of the ordinary skill in the art have to go through "undue experimentation" in order to practice the invention.

Nature of the invention and the breadth of the claims:

The scope of invention as claimed encompasses extending the blood circulatory half-life of any glycoprotein or of a glycoprotein comprising compound by removing in vitro of one or more non-sialylated O-linked carbohydrates that comprise Gal (β1-3)Gal(NAC) and/or Gal (β1-4)Gal(NAC) or by sialylating in vitro of Gal (β1-3)Gal(NAC) and/or Gal (β1-4)Gal(NAC) moieties.

Guidance of the Specification, Existence of Working Examples, State of the Art and the Predictability of the Art: With respect to invention instant specification only provides guidance and/or evidences regarding use of an a recombinant C1 inhibitor (rhC1INH) that is sialylated on O-linked carbohydrate moieties Gal (β1-3)Gal(NAC) in vitro or with non-sialylated O-linked carbohydrate carbohydrates removed and intravenously injecting to test the same for an increased half-life in plasma circulation.

However, applicant does not disclose an enabled example of any other glycoprotein or a glycoprotein comprising compound that was made to extend its

circulatory half life using said method. In the absence of representative number of enabled examples of broadly claimed subgenus of glycoproteins or the glycoprotein compounds so extended in their blood circulatory half-life, it would require undue experimentation to practice the invention in its full scope. Further the specification does not enable any other O-linked carbohydrates or carbohydrate modifying enzymes other than ST3Gal I and ST3Gal III that to increase the circulatory half life of the human C1 inhibitor.

Given the lack of predictability in the prior art regarding the functions of various asialylated carbohydrates that can be removed or sialylated using enzymes in vitro on various glycoproteins or glycoprotein comprising compounds one of skill in the art would be unable to predict a priori which or any of the broadly claimed glycoproteins or glycoprotein compounds other than the disclosed recombinant-C1INH could be made to extend the circulatory half-life. Even in case of CINH, the extended half-life is obtained only with respect to said recombinant INH but is till lower than the naturally occuring C1INH. Art at the time of invention indicates that the central question of how glycosylation contributes to the glycoprotein structure and function is not yet clear (Wang et al., 1996, Biochemistry 35:7929-7307, entire article, abstract; p.7299, col.2 bridging p.7300). Different glycoproteins differ with respect to the function of various carbohydrates moieties on them. Hence, changes in carbohydrate moieties introduced by different enzymes or chemical attachments may cause various specific effects with respect to different glycoproteins, such as in their properties of activity, intracellular trafficking, localization of protein in the cell, modification of immunological properties and other properties apart from hypothesized increasing blood circulatory half-life of a protein or the stability of said glycoprotein. Thus with the upredictability of the art regarding the role of O-glycosylation in different glycoproteins, coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the full scope of the invention as claimed i.e., increasing blood circulatory half-life of any and/or all glycoproteins by modifying a O-linked carbohydrate moiety and using any carbohydrate modifying

enzyme or specifically the Gal (β1-3)Gal(NAC) and/or Gal (β1-4)Gal(NAC) modifying enzymes.

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully predict a priori the specific effects of modifying O-glycosylation of a broadly claimed glycoproteins on extending their circulatory half-life. One of skill in the art have to experiment or conduct research for the applicant with claimed humongous genera of glycoproteins or glycoprotein comprising compounds or at least with a representative number of species belonging to this huge genera of glycoproteins claimed in order to determine, whether or if there is general applicability of the claimed method.. However, one of skill in the art would be confused if these introduced modifications in O-linked sugars bring in any other effects on the modified protein in terms of its specificity, localization or immune reactions etc. Accordingly, in view of the lack of teachings in the art and in view of insufficient guidance provided by the specification (sufficient number of examples) regarding the broad claims as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention.

Response to Arguments of 05/19/2010:

Applicant amends claims to reflect removal or sialylation modifications restricted to Gal (β1-3)Gal(NAC) or Gal (β1-4)Gal(NAC) residues on O–linked carbohydrate moieties of C1INH and/or any glycoprotein or a glycoprotein comprising compound. Applicant argues that these amendments overcome the enablement rejection of record.

Applicants' arguments are however, found not persuasive because firstly the primary Claims encompasses in its breadth extending circulatory half-life of any glycoprotein or a glycoprotein comprising compounds. However the applicant does not disclose a representative number of enabled examples of the broadly claimed glycoprotein or glycoprotein comprising compounds that were enabled with respect to claimed extension of circulatory half-life by using the method of modifcations described

for C1INH. In the absence sufficient guidance in the specification and/or the art one of ordinary skill in the art would conclude that the invention as instantly claimed is unpredictable and 'undue'. Hence the rejection is maintained with modifications and extended to new claims.

Conclusion:

No claim allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyanna Ph.D.,* whose telephone number is **(571) 272-3307**. The examiner can normally be reached Monday through Thursday from 9 AM-7PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Joseph Woitach Ph.D.*, may be reached at **(571) 272-0739.** The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). When calling please have your application serial number or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. For all other customer support, please call the USPTO call center (UCC) at (800) 786-9199.

/Robert M Kelly/
Primary Examiner, Art Unit 1633